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Clinical Study

Gemcitabine and Docetaxel for Epithelioid Sarcoma: Results from a Retrospective, Multi-Institutional Analysis

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Key Words

Sarcoma · Epithelioid sarcoma · Gemcitabine · Docetaxel · Chemotherapy · Combination chemotherapy · Soft tissue sarcoma · Palliative chemotherapy

Abstract

Objective: Epithelioid sarcoma (ES) presents unique clinical features in comparison to other sarcoma subtypes. Data regarding the benefits of chemotherapy are very limited. Combination regimens using gemcitabine and docetaxel (Gem/Doce) have proven to be effective, especially in uterine and nonuterine leiomyosarcoma. Yet, there is no available data on the efficacy of Gem/Doce in ES. **Methods:** A retrospective analysis of the three participating institutions was performed. Twenty-eight patients with an ES diagnosis presented at one of the participating institutions between 1989 and 2012. Of this group, 17 patients received chemotherapy. **Results:** Patients' median overall survival (OS) after the beginning of palliative chemotherapy was 21 months, and the 1-year OS was 87%. Twelve patients received Gem/Doce with a clinical benefit rate of 83%. The median progression-free survival (PFS) was 8 months for all patients receiving Gem/Doce. The best response was complete remission in 1 patient and partial remission in 6 patients. All 6 patients receiving Gem/Doce as a first-line treatment showed measurable responses with a median PFS of 9 months. **Conclusions:** In this retrospective study, Gem/Doce was an effective chemotherapeutic regimen for ES. Prospective studies are needed to better assess the effects of this combination drug therapy.

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Introduction

Being an extremely rare disease, epithelioid sarcoma (ES) shows unique clinical features compared to other sarcoma entities, including a high probability of recurrence and lymphatic spread [1–5]. Unfortunately, patients often develop local recurrences, even after a wide excision [6]. Data on the natural course of the disease are limited due to the rarity of ES and is mainly based on anecdotal case reports and monoinstitutional series.

Tumor grade (grade 2 vs. grade 3 according to FNCLCC) and location (classical vs. proximal type) are considered to be associated with different outcomes [7]. Other parameters like age, gender, tumor size and vascular invasion have been reported to correlate with prognosis [8].

Observations from a large cohort (441 patients from the SEER database) showed that most patients were between 17 and 60 years of age [9]. Patients with localized disease had a much better outcome than patients with regional metastases (5-year survival of 75 vs. 49%). None of the patients with distant metastases was alive at 5 years after diagnosis. The 1-year survival probability in the population with distant metastases was 46%. In terms of identifying the primary tumor's location with patient survival probability, patients with deep axial lesions fared the worst, while patients with superficial appendicular lesions had the best prognosis. Undergoing surgery seemed to be beneficial (5-year survival of 68 vs. 33% for those not undergoing surgery). Surgical excision is the treatment of choice for locally confined disease. Despite the overall poor prognosis, surgical excision should also extend to the regional lymph node metastases if present (22–29% of the patients) [10–12]. Amputation has not been shown to result in a superior outcome in regard to local control and prognosis in comparison to a wide resection [8]. Sentinel node biopsy has been proposed for patients with ES, but the results reported in the literature thus far have not been promising [13, 14]. Furthermore, radiotherapy might be able to improve local control [15].

Since many of the patients (26–69%) will eventually relapse locally, develop nodal (44%) or grossly metastatic disease (44%) [1, 16], effective chemotherapeutic options are urgently needed. Until now, no prospective randomized trials have examined the role of systemic chemotherapy, and the value of chemotherapy in this disease is still being questioned [6]. Some case series, case reports and retrospective studies reported on the therapeutic benefit of anthracyclines, ifosfamide or vinorelbine [17–19]. There is only one systematic report assessing the role of chemotherapy in the presence of distant metastases [20]. The authors conclude that systemic chemotherapy with anthracyclines/ifosfamide provides satisfactory palliation in patients with ES, but responses are of short duration. There is an unmet need for more effective and novel ES treatment strategies.

Anthracyclines are considered the standard first-line therapy in the palliative treatment of most subtypes of soft tissue sarcoma (STS). Combination regimens using gemcitabine and docetaxel (Gem/Doce) have proven to be effective in STS, especially when used in uterine and nonuterine leiomyosarcoma [21–24], but are formally not approved for STS treatment. Thus far, there are no available data on the efficacy of Gem/Doce for ES. Therefore, we performed a retrospective analysis of the three participating institutions to investigate the potential benefit of Gem/Doce in treating this disease.

Methods

From 1989 to 2012, 28 patients with an ES diagnosis presented at one of the three participating institutions (University Hospital Greifswald, Sarcoma Center Berlin-Brandenburg and University Hospital Dresden). Clinical and histopathologic data were collected by reviewing medical records and were then entered in a comprehensive database (table 1). Response was assessed using World Health Organization

Table 1. Patient characteristics
(n = 28)

Median age (range), years	35.0 (18.0–57.0)
<i>Sex</i>	
Male	21 (75%)
Female	7 (25%)
<i>Site of primary tumor</i>	
Upper limb	11 (39.3%)
Lower limb	11 (39.3%)
Trunk	6 (21.4%)
<i>Primary therapy</i>	
Resection part of therapy	24 (85.7%)
R0	8 (28.6%)
R1	12 (42.9%)
R2	4 (14.3%)
Second resection (after R1 or R2)	12 (42.9%)
Isolated limb perfusion + resection	3 (10.7%)
CTX part of therapy	5 (17.9%)
Palliative	2 (7.1%)
Neoadjuvant	1 (3.6%)
Adjuvant CTX only	1 (3.6%)
CTX + RTX	3 (10.7%)
<i>CTX (without adjuvant therapy)</i>	
1 line	17 (60.7%)
2 lines	10 (35.7%)
3 lines	5 (17.8%)
<i>RTX</i>	8 (28.6%)
Adjuvant RTX	5 (17.9%)
Adjuvant RTX + CTX	3 (10.7%)
<i>Amputation</i>	
All	9 (32.1%)
Curative intent	7 (25.0%)
Palliative intent	2 (7.1%)
<i>Site of metastases at diagnosis</i>	8 (28.6%)
Lymph node (regional)	3 (10.7%)
Pulmonary	3 (10.7%)
Skin	1 (3.6%)
Multiple	1 (3.6%)
<i>Site of metastases during course</i>	
Lymph node (not regional)	6 (21.4%)
Pulmonary	17 (60.7%)
Skin	5 (17.9%)
Multiple	2 (7.1%)
Hepar	2 (7.1%)
Bone	4 (14.3%)
<i>Local relapse</i>	9 (32.1%)
Local relapse without metastases	6 (21.4%)
CTX = Chemotherapy; RTX = radiotherapy.	

criteria and Response Evaluation Criteria in Solid Tumors (RECIST) after 2–3 cycles of chemotherapy. Radiologic images were not available for all patients and were not reviewed again for this study. Additionally, we were unable to retrieve some patients' toxicity data because we had difficulties in obtaining patient records dating back from more than 20 years ago from various institutions. The patients' records indicated that data on adverse events and toxicity were not collected in a systematic manner (i.e. according to the common toxicity criteria).

Twenty-four patients underwent primary resection with or without adjuvant chemotherapy. Four patients with widely metastatic disease at diagnosis received chemotherapy with palliative intention. One patient presented after having R2 resection elsewhere and refused further treatment.

Nineteen of 24 patients with primary resection eventually developed metastatic disease. Six of these 19 patients relapsed locally before manifestation of metastatic disease. Only 1 patient developed a local recurrence without metastatic disease. He never received chemotherapy. Three patients who initially presented with regional nodal metastases died (6, 15 and 43 months from the first presentation). Three patients were lost to follow-up.

Seventeen patients received at least one course of chemotherapy (CTX). Of those, 10 patients received second-line therapy and 5 patients also continued with third-line CTX.

The choice of the chemotherapy regimen and duration of treatment were at the discretion of the treating physician. Treatment response was evaluated by magnetic resonance imaging or computed tomography. Progression-free survival (PFS) was defined as the time from the start of chemotherapy until disease progression or death. Overall survival (OS) was defined as the time from the start of chemotherapy until death by any cause. Follow-up data for surviving patients were censored at the time of their last presentation at one of our outpatient clinics. The most frequently used regimens were anthracycline (A) ± ifosfamide (I) (13 patients) and Gem/Doce (12 patients). A ± I was mainly used as a first-line treatment (8 patients.), whereas Gem/Doce was applied as a first-line (6 patients), second-line (7 patients) and third-line (1 patient) therapy (fig. 1). One patient again received Gem/Doce as a second-line treatment after a prior very good response as a first-line treatment. All patients receiving Gem/Doce were treated with a fixed-dose rate of gemcitabine, as published by Hensley et al. [24–26]. Other chemotherapeutic agents were high-dose ifosfamide, trofosfamide, gemcitabine/cisplatin, cisplatin/dacarbazine or doxorubicin/dacarbazine.

Results

The median OS of the whole cohort from the time of the first presentation was 65 months. The median OS of patients receiving palliative chemotherapy from the time of their first presentation was 41 months. The median OS in patients from the beginning of palliative chemotherapy was 21 months (fig. 2). Twelve-month OS was 87%.

Response to Anthracycline or Anthracycline/Ifosfamide

In our retrospective analysis, 13 patients received A or A/I (8 patients as a first-line, 1 patient as a second-line and 4 patients as a third-line treatment) with a clinical benefit rate (CBR) of 46% [complete remission (CR) 0, partial remission (PR) 0 and stable disease (SD) 6 patients]. Irrespective of the treatment line, the median PFS was 3 months in patients treated with A, 8 months in patients treated with A/I and 3 months in patients who received other regimens (high-dose ifosfamide, trofosfamide, gemcitabine/cisplatin, cisplatin/dacarbazine or doxorubicin/dacarbazine).

Response to Gemcitabine/Docetaxel

Twelve patients received a total of 12 combination regimens of Gem/Doce in the course of the disease (6 patients first-line, 5 patients second-line and 1 patient third-line treatment). Ten of 12 patients had SD or better. This translates into a CBR of 83%. The median PFS was 8 months in all patients and 9 months in patients treated with Gem/Doce as a first-line treatment.

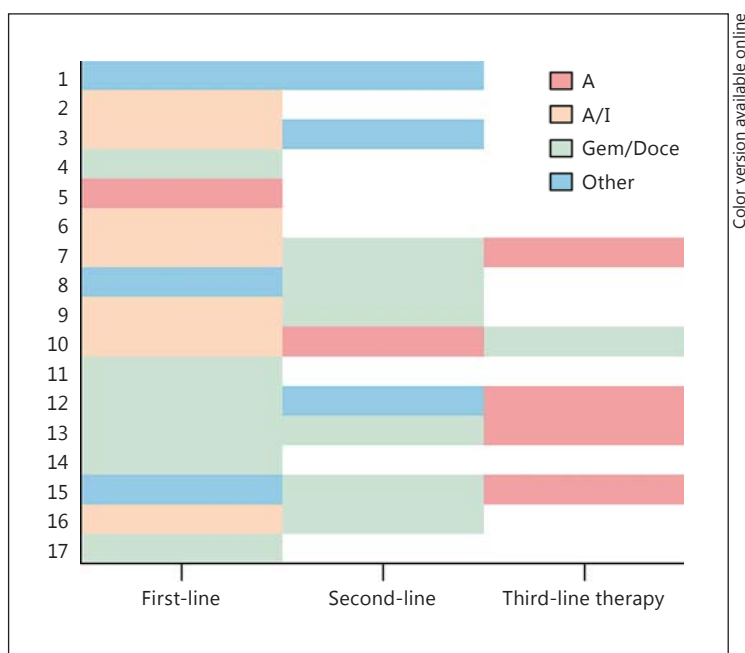


Fig. 1. The regimens used in different patients.

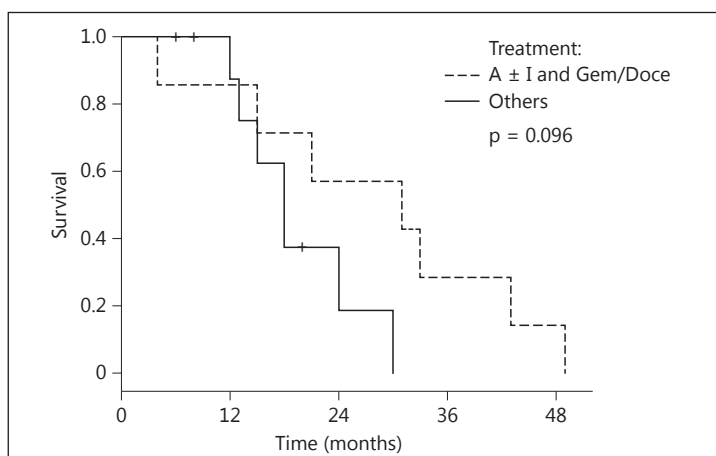


Fig. 2. Kaplan-Meier curve showing the OS of patients from the beginning of palliative CTX.

Patients responded to Gem/Doce irrespective of the line of treatment. An objective response was seen in 7 of 12 regimens of Gem/Doce and in 0 of 13 regimens of A ± I, as illustrated in figure 3, indicating that the frequency of objective response is significantly higher after Gem/Doce ($p < 0.05$, Fisher's exact test). Other regimens also did not demonstrate any objective response.

The best response to first-line treatment was CR in 1 patient and PR in 5 patients. The best response to second-line treatment was PR ($n = 1$), and even in the third-line treatment, the patient experienced disease stabilization of more than 6 months (fig. 4).

Classic versus Proximal-Type ES

Eight patients with classic ES were treated with Gem/Doce. Best responses were CR ($n = 1$), PR ($n = 4$) and SD ($n = 3$). Median PFS was 8 months. Four patients with proximal-type ES were treated with Gem/Doce. Two patients did not respond to this type of therapy [progressive disease (PD); $n = 2$], while the remaining 2 patients had PR with a PFS of 8 and 9 months, respectively.

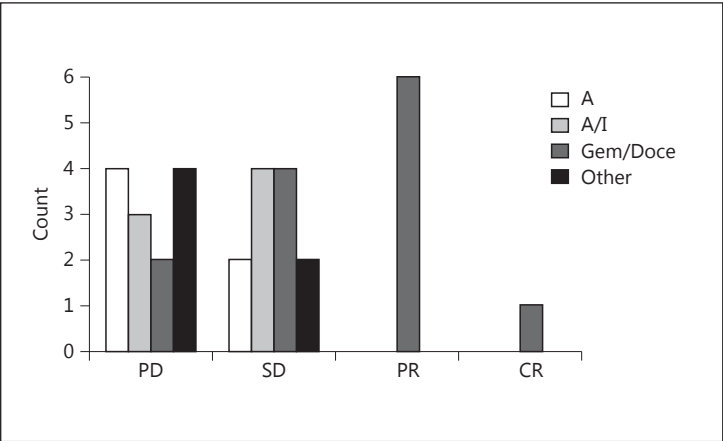


Fig. 3. Best response seen in the different regimens.

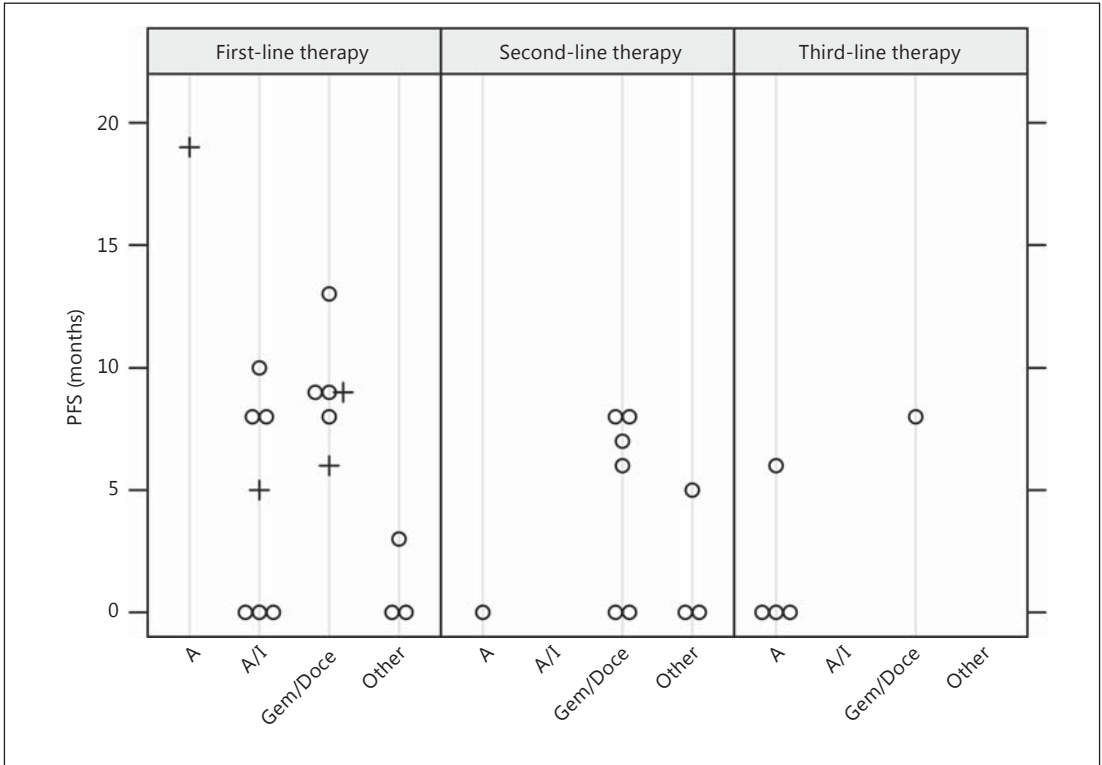


Fig. 4. PFS depending on the line of therapy and treatment. + = Censored; O = not censored.

Discussion

Until now, no prospective randomized trial examining the role of systemic chemotherapy in ES has been published. Due to the rarity of the disease, the only data available stem from some case series, case reports and retrospective studies [17–19].

Anthracyclines are considered the standard first-line chemotherapeutic agent in most STS subtypes. The most frequently used regimens in ES include anthracyclines and ifos-

famide. One of the two available retrospective studies was performed to evaluate the clinical features, the management and the outcome of pediatric and adolescent patients with ES [20]. Thirty patients over the age of 18 with ES who were enrolled in the Italian Soft Tissue Sarcoma Committee protocols were included. Eight of these 30 patients were treated with systemic chemotherapy over the course of their disease (2 patients with anthracyclines but no ifosfamide, 6 patients with regimens including ifosfamide and anthracyclines). The response to primary chemotherapy was evaluable in 7 patients and was CR in 2 patients, PR in 1 patient, and SD in 4 patients accounting for an overall response rate of 43%. All 3 patients who responded to chemotherapy had received combination regimens including ifosfamide and anthracyclines.

The retrospective study by Jones et al. [17] was performed to assess the role of chemotherapy for ES patients with distant metastases and, to our knowledge, is the only study to address this question that has been published to date. The study reported on 21 patients with ES, treated with chemotherapy between 1990 and 2009 at a single referral center. The patients' most commonly chosen regimens were single-agent doxorubicin and doxorubicin in combination with ifosfamide. The response to first-line chemotherapy was evaluable in 20 patients. Three patients had PR, 12 patients SD and 5 patients PD. All objective responses were seen in patients with classic-type ES. The median PFS was 29 weeks, and the 6-month progression-free rate was 53%. The median OS from commencing palliative chemotherapy was 51 weeks, and the 12-month OS probability amounted to 46%.

The authors concluded that their results, and those of the Italian group reported beforehand, suggest that some of the patients with ES benefit from palliative chemotherapy with A and A/I.

In our series, 13 patients received A or A/I (8 patients as a first-line, 1 patient as a second-line and 4 patients as a third-line treatment) with a CBR of 46% (CR 0, PR 0 and SD 6 patients). The median PFS was 8 months across all lines of therapy. Although no patient in our study showed an objective response to A or A/I, our data are consistent with the results of the retrospective study of Jones et al. [17] in terms of the CBR and the median PFS. A relevant proportion of patients in our study (46%) and in the study of Jones et al. [17] (75%) achieved at least disease stabilization for more than 6 months (median PFS of 8 and 6.6 months, respectively).

In our analysis, 10 of 17 (59%) patients had at least one further treatment after first-line therapy failed, which differs from the study of Jones et al. [17], in which only 7 of 21 (33%) patients received further treatment after first-line therapy. Furthermore, the best-documented response in second-line CTX in Jones' study was SD in 2 patients, lasting 5 and 11 months, respectively.

The median OS after the start of palliative chemotherapy in our study was 21 months, the 1-year OS was 87%. These results suggest that adding Gem/Doce to the treatment plan of patients with metastatic ES may have improved the outcome of our patient cohort, especially considering that patients in our study receiving Gem/Doce had a median PFS of 8 months. However, it should be noted that, given the retrospective nature of our analysis, a selection bias cannot be excluded.

Looking at patients' response to Gem/Doce across all lines of therapy, we found that 7 of 12 patients achieved at least a PR, while CBR amounted to 83% (10 of 12 patients). Our study indicates a comparable median PFS of 8 months for the advanced ES patients receiving either A/I or Gem/Doce. Notably, all 6 patients receiving Gem/Doce as a first-line treatment showed measurable responses (median PFS of 9 months) in comparison to the lack of measurable responses for the 7 patients treated with the combination regimen of A/I (median PFS of 8 months).

Patients with classic ES and with proximal-type ES responded to Gem/Doce. PFS of responding patients was comparable in both groups, but the numbers were too small for

further conclusions. It is important to note that Gem/Doce is currently not approved for the treatment of STS.

To date, no second-line treatment regimen, following the failure of A/I, has been shown to be active in metastatic ES.

The present study has some limitations. It is important to consider the relatively small number of patients in the study when drawing conclusions from the data. Apart from the above-mentioned possibility of a selection bias, a radiologic review of response by RECIST criteria could not be performed in all patients, so some patients with clinical PR might not have met the formal criteria for response. Moreover, patients were treated with Gem/Doce across different lines of therapy, which could be another limitation in interpreting the results. We were also unable to systematically collect data regarding the toxicity of Gem/Doce and patients' quality of life. The main aim of this study was to investigate the efficacy of Gem/Doce in ES, since the adverse events and toxicity profile have been well described in other studies [21, 23–26]. The most frequently occurring adverse events were hematologic, with some patients requiring a dose reduction. In our study, there were no treatment discontinuations due to toxicity. Clearly, a prospective randomized trial would be able to provide more solid data on the efficacy of the regimen. However, given the rarity of the disease, it would be very challenging to perform such a study.

In conclusion, our retrospective analysis not only demonstrates that patients with metastatic ES benefit from palliative chemotherapy but also that Gem/Doce is a promising chemotherapeutic regimen in ES treatment. Adding Gem/Doce to the armamentarium of antiproliferative drugs may improve OS in ES patients with metastatic disease.

Disclosure Statement

The authors have no conflicts of interest to declare.

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